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Clinical improvement upon rituximab treatment in a patient with verrucous cutaneous discoid lupus erythematosus

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Introduction

Discoid lupus erythematosus (DLE) is the most prevalent manifestation of chronic cutaneous lupus erythematosus; other clinical manifestations are lupus profundus, lupus panniculitis, lupus tumidus, lupus erythematosus verrucosus and chilblain lupus[1]. There are no reliable evidence-based treatment recommendations available[2], but typical first-line treatment options consist of sun protection, topical corticosteroids, and antimalarial drugs; therapy-resistant cases are usually treated with immunesuppressive drugs such as azathioprine, mycophenolate mofetil, or cyclophosphamide[1]. Depletion of CD20-positive B cells has been reported to be effective in systemic lupus erythematosus SLE[3-5], but two recent clinical trials did not show a positive effect of rituximab (anti-CD20 antibody, RTX) in SLE[6, 7].
Here, we report a clinical response in a patient with a therapy-refractory hypertrophic chronic discoid lupus erythematosus upon treatment with RTX.

Case report

The then 22 year old patient was diagnosed in 1986 with hypertrophic, partly verrucous form of DLE on the face, scalp, neck and the distal upper extremities. UV exposure led to worsening of the lesions. ANA (highest titer measured 1:320), anti-SSA (13), and anti-SSB (1), as well as anti-dsDNA (5) and the normal C3 and C4 values did never insinuate a development of a SLE. Accordingly, neither pathologic hematologic and urine tests nor clinical signs of systemic involvement were present at any time during the long observation period of the disease.
The patient showed initially small plaques on face, scalp and arms, which, over time, became confluent and hypertrophic. Compliance was believed to be insufficient, and neither nicotine abuse nor sun exposure during working hours as a mason was efficiently ceased or reduced. The biopsy showed interface dermatitis in association with a pseudoepitheliomatous hyperplasia of the epidermis, vacuolization of the junction zone and apoptotic keratinocytes. Focal mucin deposits were detectable in the alcian blue stain (figure 1).
Over the years, the patient was treated with topical steroids, hydroxychloroquine, prednisone in conjunction with azathioprine, isotretinoin or acitretin, systemic prednisone, mycophenolate mofetil, and radiotherapy on selected hypertrophic areas, but to no effect at all or no lasting effect. Based on reports in the literature [8], we treated the patient with efalizumab from February 2008 till april 2009, when the drug was retracted from the market due to rare incidences of progressive multifocal leukencephalopathy. During the first 4 months of efalizumab treatment (1mg/kg/week), the patient was weaned from systemic prednisone and mycophenolate mofetil. Erythema, scaling, and dermal induration improved, and the patient reported that his skin felt much less thickened and inflamed. Upon cessation of efalizumab, the symptoms rebounded, and he was put back on mycophenolate mofetil and prednisone. And intercurrent radiotherapy with anti-inflammatory dosage of 6x1Gy, 30kV on the lower arm did not improve the dermatitis in the radiation field, and further irradiations were not pursued.
The patient was included in a afamelanotide study (implantation of a synthetic analog of the naturally occurring alpha-melanocyte stimulating hormone (α-MSH) in june 2011, and august 2011), aiming at a reduced photosensitivity due to increased intrinsic melanin production, but again, there was no significant clinical response to this experimental treatment. Due to the development of 2 squamous cell carcinoma on the penis and on the forearm, we were aiming at reducing the immunosuppression with prednisone and mycophenolate mofetil. In May 2013, the patient had a CLASI Total Activity/Total Damage Score of 19/10, and we started with rituximab infusion according to the rheumatologic infusion scheme (1000mg/infusion on day 1 and day 15), and reduced prednisone/mycophenolate mofetil gradually. Upon the first

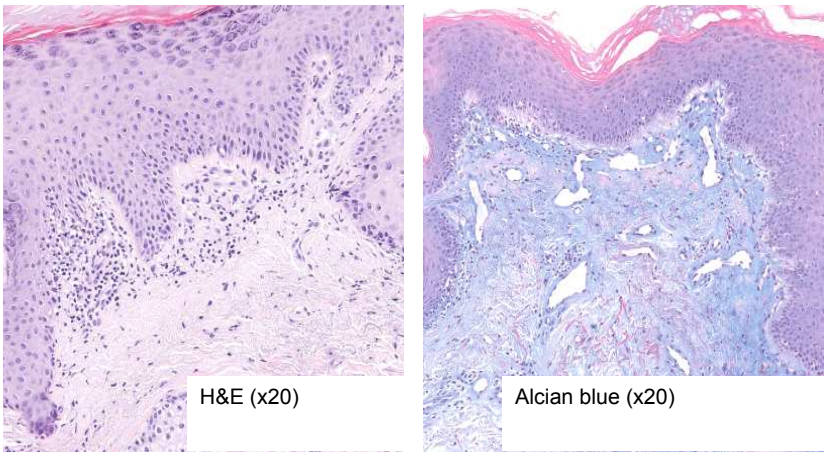

Fig. 1: Chronic discoid lupus erythematosus CDLE:
A) pseudoepitheliomatous hyperplasia of the epidermis and interface dermatitis with basal layer vacuolar changes, and apoptotic keratinocytes. Mononuclear (predominantly T cells) dermal inflammatory infiltrate.
B) focal dermal mucine deposits in alcian blue stain.

Report

	Intercellular substance	Nuclei	Basal-membrane	Vessel wall
Fibrinogen	-	-	-	-
C3	-	-	+	-
IgG	-	-	+	-
IgA	-	-	-	-
IgM	-	-	+	-

Table 1: Immunofluorescence microscopy of CDLE: Lupusband with linear Immunglobuline and C3 deposits along the basal membrane (cave: false positivity on sun-exposed skin and negative results in long-standing chronic LE lesions)

infusion, inflammation of the involved skin was significantly reduced and the patient reported much less scaling and redness (CLASI Score reduction to 10/10). Currently, the patient does not take any prednisone/mycophenolate mofetil awaits the second infusion treatment upon recent ~~and~~ increase of peripheral CD19/20 positive B-cells.

Discussion

Chronic discoid lupus erythematosus (chronic cutaneous lupus erythematosus, CDLE, CCLE) develop in approximately one fourth of SLE patients, but may also occur isolated [9]. Patients with isolated CDLE lesions usually have a negative or low antinuclear antibody (ANA) titer with rare increase of SSA/SSB antibodies [10]. Patients with extended cutaneous lesions and longer and therapy-refractory course of disease are at higher risk to develop SLE [11] [12]. As CDLE may become hyperkeratotic, it may be confused with hypertrophic lichen ruber, prurigo nodularis, keratoacanthoma disseminatum, or even, at an early stage, with eczema or psoriasis. Histology at early stage is important to differentiate between CDLE and other chronic dermatitis, as UV light should be avoided in the former, but is frequently used to treat the latter. Skin biopsy with direct immunofluorescence (with detection of linear IgG, IgA, IgM, C1 and C3 deposits, lupusband) in non-sun-exposed areas helps establishing the diagnose.

Given the photosensitivity of the disease and the lack of large scale trials addressing the efficacy of sunscreens in the management of cutaneous lupus, patients should be advised to use broad spectrum, water-resistant sunscreens with an SPF of at least 30, better 50+. Beside the topical treatment with potent steroids, and calcineurin inhibitors in less active intervals, intralesional injection of triamcinolone crystal suspension has been described as an efficient local treatment in recurrent disease, but with low evidence[2]. First-line systemic treatment consists in hydroxychloroquine which leads to a reduction HLA-DR+/CD1a+ cells in lesional skin and reduced antigen presentation [13] [14]. In our patient, hydroxychloroquin (Plaquenil ®) did not show any effect, but the patient never ceased his nicotine abuse, which is believed to reduce efficiency of the drug [15] [16] by interfering with uptake of drug into cell lysosomes or an accelerated metabolic clearance of this medication. There is no randomized controlled clinical trial (RCT) data for the use of azathioprine, mycophenolate mofetil (MMF), systemic cortisone for treatment of CDLE, and neither is there an RCT for efalizumab or any other biologic with T-cell inhibitory effect. When efalizumab was retracted from the market due to rare events of progressive multifocal leukencephalopathy, we did not use any other antipsoriatic drug, as, in contrast to efalizumab, the TNF-blockers have been described to induce a lupus-like syndrome [17].

The anti-CD20 antibody rituximab has been approved in Switzerland for treatment of B-cell lymphoma, rheumatoid arthritis, and ANCA-associated vasculitis; however, it has been used for a series of dermatologic disorders, such as pemphigus vulgaris, bullous pemphigoid, dermatomyositis and lupus variants. In a recent review of the literature [18], RTX effect on cutaneous symptoms in cutaneous lupus, in a second line setting, was reported to be 80% complete response (8/10 patients), and 20% partial response (2/10 patients). Three patients developed a relapse within 12 months, but their skin cleared again by an additional cycle of RTX [18]. Three patients suffered from SLE, whereas five patients had SCLE, and only one patient had CDLE (one patient not classified). According to the literature, it appears that B-cell depletion is particularly beneficial in skin lesions of SLE, in SCLE, and to a lesser extent only in CDLE. It has been speculated that pathogenesis of CDLE may not be the same as in SLE, which may be mirrored in the increased B-cell activity with increased ANA and antinuclear or anti-cytoplasmic antibodies

in SLE compared to CDLE [19].
The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) was used to assess treatment success. CLASI differentiates between disease activity and damage in 2 separate scores. The activity scale includes measurements of erythema, scale and hypertrophy in defined body regions, and mucous membrane disease, whereas the damage scale measures hyperpigmentation, atrophy, and scarring alopecia in the same regions[20] [21]. This separation is unusual for dermatological scores, but useful for inflammatory disorders that may leave a permanent damage on the tissue, i.e. atrophy or scars. This distinction between activity and damage is established for the scoring of SLE. Our patient responded to the RTX treatment with a reduction of the inflammatory activity, but the inflicted damage of the decade-long course of disease could obviously not be reversed, hence the unchanged damage score.

In summary, we report on a single case with therapy-refractory chronic discoid lupus erythematosus withous systemic involvement who responded beneficially towards a first cycle of rituximab infusion according to the rheumatologic dosage of 2x1000mg in 2 weeks interval.

References:

1. Kuhn, A., V. Ruland, and G. Bonsmann, Cutaneous lupus erythematosus: update of therapeutic options part I. J Am Acad Dermatol, 2011. 65(6): p. e179-93.
2. Jessop, S., D.A. Whitelaw, and F.M. Delamere, Drugs for discoid lupus erythematosus. Cochrane Database Syst Rev, 2009(4): p. CD002954.
3. Lu, T.Y., et al., A retrospective seven-year analysis of the use of B cell depletion therapy in systemic lupus erythematosus at University College London Hospital: the first fifty patients. Arthritis Rheum, 2009. 61(4): p. 482-7.
4. Ramos-Casals, M., et al., Rituximab in systemic lupus erythematosus: A systematic review of off-label use in 188 cases. Lupus, 2009. 18(9): p. 767-76.
5. Terrier, B., et al., Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French AutoImmunity and Rituximab registry. Arthritis Rheum, 2010. 62(8): p. 2458-66.
6. Looney, R.J., B cell-targeted therapies for systemic lupus erythematosus: an update on clinical trial data. Drugs, 2010. 70(5): p. 529-40.
7. Merrill, J., et al., Assessment of flares in lupus patients enrolled in a phase II/III study of rituximab (EXPLORER). Lupus, 2011. 20(7): p. 709-16.
8. Clayton, T.H., S. Ogden, and M.D. Goodfield, Treatment of refractory subacute cutaneous lupus erythematosus with efalizumab. J Am Acad Dermatol, 2006. 54(5): p. 892-5.
9. Pistiner, M., et al., Lupus erythematosus in the 1980s: a survey of 570 patients. Semin Arthritis Rheum, 1991. 21(1): p. 55-64.
10. Provost, T.T., The relationship between discoid and systemic lupus erythematosus. Arch Dermatol, 1994. 130(10): p. 1308-10.
11. Callen, J.P., Systemic lupus erythematosus in patients with chronic cutaneous (discoid) lupus erythematosus. Clinical and laboratory findings in seventeen patients. J Am Acad Dermatol, 1985. 12(2 Pt 1): p. 278-88.
12. Rowell, N.R., Laboratory abnormalities in the diagnosis and management of lupus erythematosus. Br J Dermatol, 1971. 84(3): p. 210-6.
13. Callen, J.P., Chronic cutaneous lupus erythematosus. Clinical, laboratory, therapeutic, and prognostic examination of 62 patients. Arch Dermatol, 1982. 118(6): p. 412-6.
14. Ruzicka, T., et al., Treatment of cutaneous lupus erythematosus with acitretin and hydroxychloroquine. Br J Dermatol, 1992. 127(5): p. 513-8.
15. Jewell, M.L. and D.P. McCauliffe, Patients with cutaneous lupus erythematosus who smoke are less responsive to antimalarial treatment. J Am Acad Dermatol, 2000. 42(6): p. 983-7.
16. Rahman, P., D.D. Gladman, and M.B. Urowitz, Smoking interferes with efficacy of antimalarial therapy in cutaneous lupus. J Rheumatol, 1998. 25(9): p. 1716-9.
17. Aringer, M. and J.S. Smolen, Therapeutic blockade of TNF in patients with SLE-promising or crazy? Autoimmun Rev, 2012. 11(5): p. 321-5.
18. Hofmann, S.C., et al., Effects of rituximab-based B-cell depletion therapy on skin manifestations of lupus erythematosus--report of 17 cases and review of the literature. Lupus, 2013. 22(9): p. 932-9.
19. Werth, V.P., Cutaneous lupus: insights into pathogenesis and disease classification. Bull NYU Hosp Jt Dis, 2007. 65(3): p. 200-4.
20. 20. Albrecht, J. and V.P. Werth, Development of the CLASI as an outcome instrument for cutaneous lupus erythematosus. Dermatol Ther, 2007. 20(2): p. 93-101.
21. 21. Bonilla-Martinez, Z.L., et al., The cutaneous lupus erythematosus disease area and severity index: a responsive instrument to measure activity and damage in patients with cutaneous lupus erythematosus. Arch Dermatol, 2008. 144(2): p. 173-80.

Test	Results [Highest/ lowest values]	unit	Reference values
Rheuma factor	<10	IE/ml	<20
ANA	1:320	Titer	<1:10
Anti-native DNS	18	IE/ml	<20
Anti-Chromatin	4	E/ml	<20
Anti-Histon	0.1	IE/ml	<1.0
Anti-SS-A	13	E/ml	<5
Anti-SS-B	1	E/ml	<5
Kompl. Factor C3c	1.30	g/l	0.90-1.80
Kompl. Factor C4	0.35	g/l	0.10-0.40
Immunkompl. C1q-Bdg.	1	% Bdg.	<2
Immunkompl. IgG	1	mg/l	1-10
Anti Sm	0	E/ml	<10
Interleukine-6	5.7	pg/ml	<3.1
IgG	8.6	g/l	7.0-16
IgM	0.6	g/l	0.4-2.3

Table 2: Serological tests